Parkinson's Disease and Its Management

Part 1: Disease Entity, Risk Factors, Pathophysiology, Clinical Presentation, and Diagnosis

George DeMaagd, PharmD, BCPS; and Ashok Philip, PhD

INTRODUCTION

Parkinson's disease (PD) was first described by Dr. James Parkinson in 1817 as a "shaking palsy." It is a chronic, progressive neurodegenerative disease characterized by both motor and nonmotor features. The disease has a significant clinical impact on patients, families, and caregivers through its progressive degenerative effects on mobility and muscle control. The motor symptoms of PD are attributed to the loss of striatal dopaminergic neurons, although the presence of nonmotor symptoms supports neuronal loss in nondopaminergic areas as well. The term *parkinsonism* is a symptom complex used to describe the motor features of PD, which include resting tremor, bradykinesia, and muscular rigidity. PD is the most common cause of parkinsonism, although a number of secondary causes also exist, including diseases that mimic PD and drug-induced causes.[1–3]

Research suggests that the pathophysiological changes associated with PD may start before the onset of motor features and may include a number of nonmotor presentations, such as sleep disorders, depression, and cognitive changes. Evidence for this preclinical phase has driven the enthusiasm for research that focuses on protective or preventive therapies.[4]

PD is one of the most common neurodegenerative disorders. The Parkinson's Disease Foundation reports that approximately 1 million Americans currently have the disease.[5] The incidence of PD in the U.S. is approximately 20 cases per 100,000 people per year (60,000 per year), with the mean age of onset close to 60 years. The prevalence of PD is reported to be approximately 1% in people 60 years of age and older and increases to 1% to 3% in the 80-plus age group. However, an important caveat associated with these numbers is that they do not reflect undiagnosed cases.[6,7]

Although it is primarily a disease of the elderly, individuals have developed PD in their 30s and 40s.[7] Gender differences pertaining to the incidence of PD are reflected in a 3:2 ratio of males to females, with a delayed onset in females attributed to the neuroprotective effects of estrogen on the nigrostriatal dopaminergic system.[8,9]

PD's variable but pronounced progression has a significant impact on patients, families, and society. Advanced and end-stage disease may lead to serious complications, including pneumonia, which are often associated with death.[10,11] Current treatment is focused on symptomatic management.[12,13] Evidence suggests that PD patients may also benefit from a multidisciplinary approach to care that includes movement specialists, social workers, pharmacists, and other health care practitioners.[14,15]

Numerous risk factors and genetic mutations are associated with PD. Risk factors for the disease include oxidative stress, the formation of free radicals, and a number of environmental toxins (Table 1).[16,17] Limited data support genetic associations with PD, with some gene mutations identified (Table 2).[18–20] Interestingly, an inverse relationship exists between cigarette smoking, caffeine intake, and the risk of developing PD. Inhibition of the enzyme monoamine oxidase (MAO) may explain the protective effects of tobacco smoking, whereas the benefits of caffeine may be related to its adenosine antagonist

Table 1 Risk Factors Associated With Parkinson's Disease[16–20,22,23,29–38]

- Elevated cholesterol
- Environmental toxins
  - Carbon disulfide
  - Cyanide
  - Herbicides
  - Methanol and organic solvents
  - Pesticides
- Head trauma
- High caloric intake
- Increased body mass index
- Inflammation associated with activation of microglia
- Methcathinone (manganese content)
- Methamphetamine/amphetamine abuse
- Mitochondrial dysfunction
- Nitric oxide toxicity
- Oxidative stress
  - Formation of free radicals (e.g., hydrogen peroxide)
  - Potent neurotoxins (e.g., 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)
- Post-infection states
- Signal-mediated apoptosis

Table 2 Gene Mutations Associated With Parkinson's Disease[16–20,22,23,29–38]

- Alpha-synuclein gene (*SNCA*)
- Eukaryotic translation initiation factor 4 gamma 1 gene (*EIF4G1*)
- Glucocerebrosidase gene (*GBA*)
- Leucine-rich repeat kinase 2 (*LRRK2*) gene loci
- PTEN-induced putative kinase 1 (*PINK1*) gene loci
- Superoxide dismutase 2 gene (*SOD2*)
- Vacuolar protein sorting 35 homolog gene (*VPS35*)

Dr. DeMaagd is the Associate Dean of Academic Administration and a Professor of Pharmacy Practice at the Union University School of Pharmacy in Jackson, Tennessee. Dr. Philip is an Associate Professor of Pharmaceutical Sciences at the Union University School of Pharmacy.

Disclosure: The authors report no commercial or financial interests in regard to this article.

activity.[21] The variable prevalence of PD throughout the world suggests that environmental and genetic factors along with ethnic differences may all play a role in disease pathogenesis.[22,23] Biomedical research in individuals with PD continues and may help to identify additional risk factors and to guide future prevention and treatment decisions.[24–28]

PATHOPHYSIOLOGY

PD is a disorder of the extrapyramidal system, which includes motor structures of the basal ganglia, and is characterized by the loss of dopaminergic function and consequent diminished motor function, leading to clinical features of the disease.[4,30] Research in the late 1950s identified striatal dopamine depletion as the major cause of the motor symptoms of PD, although the presence of nonmotor features supports the involvement of other neurotransmitters of the glutamatergic, cholinergic, serotonergic, and adrenergic systems, in addition to the neuromodulators adenosine and enkephalins.[39–44] Further evidence suggests that PD may originate in the dorsal motor nucleus of the vagal and glossopharyngeal nerves and in the anterior olfactory nucleus, suggesting a disease pattern that begins in the brain stem and ascends to higher cortical levels.[45] The histopathological features of PD include the loss of pigmented dopaminergic neurons and the presence of Lewy bodies (LBs).[46,47]

Progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc), which project to the striatum (the nigrostriatal pathway), results in the loss of dopaminergic function in individuals with PD. Typically, patients experience the motor features of PD only after 50% to 80% of dopaminergic neurons have been lost, suggesting the involvement of a compensatory mechanism in the early stages of the disease. Two types of dopamine receptors, D_1 (excitatory type) and D_2 (inhibitory type), influence motor activity in the extrapyramidal system. Components of this system include the basal ganglia, which involves the internal globus pallidal segment (GPi) of the ventral striatum, and the pars reticulata portion of the substantia nigra (SNpr). These components are part of larger circuits located in the thalamus and the cortex. The loss of dopamine in the striatum of PD patients results in increased activity in the GPi/SNpr circuits and subsequent gamma aminobutyric acid (GABA) dysfunction, leading to inhibition of the thalamus. The end result is the decreased ability of the thalamus to activate the frontal cortex, resulting in the decreased motor activity characteristic of PD. Accordingly, restoring dopamine activity in the striatum through D_2 and D_1 receptor activation with dopaminergic therapies mediates clinical improvement in the motor symptoms of PD.[48] In addition, dopaminergic loss results not only in reduced activation of the thalamus but also in increased cholinergic activity due to the loss of dopamine's normal inhibitory influence.[49,50] Research continues to support evidence that PD involves a diffuse global network dysfunction at multiple levels in the nervous system.[51]

The other major histopathological feature of PD is the presences of LBs, described as intracellular cytoplasmic aggregates composed of proteins, lipids, and other materials. LBs have also been identified as major hallmarks associated with chronic neurodegenerative diseases, including PD.[45,52] In patients with PD, LBs are found in dopaminergic neurons in the substantia nigra as round bodies with radiating fibrils.[46,47] Research has suggested that their formation may be secondary to refractory proteolytic processes involving abnormal breakdown or overproduction influenced by genetic mutations.[45–47] Gene mutations involving the alpha-synuclein (αSyn) protein have been found to aggregate and form insoluble fibrils associated with LBs;[53] αSyn proteins have been identified as a potential target for future PD therapy.[54]

The formation of LBs involves excessive production of misfolded forms of ubiquitin proteins, which are involved in protein recycling. The accumulation of these proteins is secondary to malfunctioning of the ubiquitin proteasome system (UPS).[52,55] The formation of LBs appears to have a role in the neurodegeneration that is characteristic of PD, with various lesion patterns seen at different stages of the disease. Lesion patterns in the dorsal nucleus, medulla, and pons may support early (premotor) olfactory and rapid eye movement (REM) features of PD. Lesions in the nigrostriatal region during later stages of the disease contribute to the common motor features of PD.[56,57] LBs are also associated with the dementia of PD, similar to their presence in patients with dementia with LBs (DLB). PD and DLB are differentiated by their clinical presentations in that motor features are more prominent and occur earlier in PD compared with DLB.[47,52,55]

Although amyloid beta 1-42 is associated with Alzheimer's disease (AD) and its pathology, recent data suggest that cerebral spinal fluid containing this biomarker may predict cognitive decline in PD as well.[58,59] These data are consistent with previous research, which reported that the pathology of AD contributes to cognitive impairment in PD and may have relevance in predicting the cognitive decline associated with PD.[58]

The involvement of inflammation in the pathogenesis of PD is also being studied, especially the role of cytokines and other mediators. Inflammatory responses secondary to the degeneration of dopaminergic neurons may play a role in PD and contribute to its pathogenesis. *In vitro* data have supported the activation of microglia and astrocytes secondary to injured dopaminergic neurons.[60–64]

In summary, PD is a complex neurodegenerative disease involving an array of molecular pathways, all of which may be implicated in the neuropathophysiology of the disease.[60]

DIAGNOSIS

The differential diagnosis of PD should include a comprehensive history and physical examination. Difficult or questionable cases should be referred to a movement-disorder specialist for further evaluation. There are no definitive tests to confirm the diagnosis of PD; therefore, a clinical diagnosis requires the clinician to review the patient's history, to assess symptoms, and to rule out alternative diagnoses, such as multiple-system atrophy, DLB disease, and essential tremor (Table 3).[65–70]

The cardinal motor features of PD—described as the "classical triad"—include a 4-Hz to 6-Hz resting tremor, "cogwheel" rigidity, and bradykinesia (Table 4). These cardinal features are often reported as the first clinical findings of the disease. A fourth feature, postural instability (Table 4), occurs in approximately 50% of PD patients within five years of diagnosis.[71–77] Although PD is considered to be a disease of the elderly, some genetic variants are present in younger patients. Clinically, younger individuals (under 60 years of age) may present with

Table 3 Diseases and Conditions That May Require Differentiation From Parkinson's Disease[65–79]

- Alzheimer's disease
- Basal ganglia tumor
- Benign essential tremor
- Cerebrovascular disease
- Corticobasal degeneration
- Creutzfeldt–Jakob disease
- Dementia with Lewy bodies
- Drug-induced parkinsonism
- Metabolic causes (e.g., hypoparathyroidism, thyroid dysfunction, nutritional deficiencies)
- Multiple-system atrophy
- Normal-pressure hydrocephalus
- Olfactory dysfunction
- Olivopontocerebellar atrophy
- Post-traumatic brain injury Parkinson's disease
- Progressive supranuclear palsy
- Shy–Drager syndrome
- Subdural hematoma
- Wilson's disease

Table 4 Motor Symptoms of Parkinson's Disease[71–78,90–101,120–128]

Cardinal Motor Features ("Classical Triad")

- Bradykinesia
  - Occurs in 80% to 90% of patients
  - Slowness of movement
  - Decreased amplitude of movement
- Rigidity
  - Occurs in 80% to 90% of patients
  - Resistance to passive movement in both flexor and extensor muscles with limb relaxed
  - Often accompanied by "cogwheel" phenomenon
- Tremor at rest
  - Common initial symptom (70% to 90% of patients)
  - Often resolves with action or during sleep
  - Primarily distal, involving hands
  - May also involve jaw, tongue, lips, chin, or legs

Other

- Postural instability
  - Predisposes patients to falls and injuries
  - Occurs in later stages of Parkinson's disease
  - Results from loss of postural reflexes
- Dysarthria
- Dystonia

less rigidity and bradykinesia, and this may result in a delayed or missed diagnosis.[76,77]

Identifying diseases that have presentations similar to those of PD is an important component of the diagnostic process. Table 3 lists some of the diseases and conditions that should be a part of the differential diagnosis and that may require additional diagnostic tests to rule out their involvement. Benign essential tremor, a common presentation, usually appears as an intention-type tremor (tremor with movement) and has greater head involvement.[71–77] DLB may present with features of PD, although patients with DLB usually experience concurrent cognitive changes and visual hallucinations.[78] Many other conditions mimic PD and may require evaluations by experts in movement disorders to confirm the diagnosis. In addition, laboratory studies may be necessary to rule out nutritional deficiencies and other abnormalities, including thyroid disease, along with toxin screening when the patient's history suggests possible exposure. The measurement of plasma levels of copper and ceruloplasmin may also be warranted to rule out Wilson's disease.[71,72,75,79] Other diagnostic procedures include bedside dopaminergic challenge tests with levodopa or apomorphine, although their use is not supported by some neurology experts.[72–75] Additional diagnostic aids may include neuropsychiatric testing, sleep studies, and vision exams secondary to visual changes reported in some PD patients, such as abnormal color vision due to changes in intraretinal dopaminergic transmission.[71,72]

Drug-induced parkinsonism (DIP) should be considered in the differential diagnosis of PD because it is one of the few reversible causes of the disorder. Identifying DIP is important in order to avoid treating patients inappropriately and therefore necessitates a complete medication evaluation in all patients suspected of having PD. High-risk populations for DIP include elderly women, patients with multiple comorbidities, and patients taking multiple medications at high doses for extended periods.[80,81]

The drugs most commonly associated with DIP include those with dopamine receptor–blocking properties, such as the antipsychotic agents haloperidol, thiothixene, and risperidone.[82–85] If PD patients require antipsychotic agents, those with a lower risk for DIP, such as quetiapine and clozapine, are recommended.[84,85] Antiemetics that contain a phenothiazine core (e.g., prochlorperazine or promethazine) and the gastrointestinal prokinetic agent metoclopramide are also associated with DIP.[80,81,86] Many other medications may also cause DIP, including some antihypertensive agents, such as methyldopa and calcium-channel blockers, along with antidepressants, lithium, and anticonvulsant drugs.[80,81,87]

The management of DIP involves identifying and discontinuing the contributing medication(s), which usually resolves the symptoms, although in some cases these may linger for a few months or up to a year or two.[81,82]

A challenge in diagnosing PD is that the disorder's clinical motor features may not present until approximately 50% to 80% of dopaminergic neurons are lost. Unfortunately, at this point significant disease progression may already exist.[88–90] Adding to this problem is the need to identify subtle motor features that can easily go unrecognized, such as the absence of arm swing or jerking motions.[91–93] Further complicating an early diagnosis is the presence of nonmotor comorbidities, including depression, anxiety, fatigue, constipation, anosmia, and sleep disorders (Table 5), which the clinician may not recognize as being associated with PD.[4,94–97] Early recognition of these features and their possible association with PD may facilitate an earlier diagnosis.[90–93] Since the onset of motor features is the point at which PD is usually diagnosed and treatment is initiated, investigators continue to search for biomarkers that may allow a more expeditious diagnosis.[101–111] Once the diagnosis of PD has been confirmed, patients who receive

Table 5 Nonmotor Symptoms of Parkinson's Disease[71–78,90–101,120–128]

Autonomic Dysfunction[a]
• Constipation (parasympathetic nervous system cholinergic) • Orthostatic hypotension (sympathetic nervous system noradrenergic) • Sexual dysfunction (parasympathetic nervous system cholinergic) • Sweating (sympathetic nervous system cholinergic) • Urinary retention (parasympathetic nervous system cholinergic)
Neuropsychiatric Symptoms
• Anxiety • Cognitive impairment (mild) • Dementia • Depression (e.g., dysphoria, suicidal ideation, apathy) • Impulse-control disorders (e.g., preoccupations, hypersexuality, compulsive shopping, binge eating)[b] • Panic disorder • Psychosis (e.g., hallucinations, delusions)
Sensory Symptoms
• Olfactory dysfunction (hyposmia) • Paresthesias • Pain
Sleep Disturbance[c]
• Daytime somnolence • Insomnia • Rapid eye movement disorder • Restless legs syndrome • Sleep attacks • Sleep apnea
Other
• Fatigue • Sialorrhea • Weight loss

[a] Depends on components of nervous system that are affected.
[b] Usually associated with use of dopamine agonists.
[c] Complex etiology; linked to neurodegenerative process, motor features, and drug therapy.

appropriate treatment may have a life expectancy similar to that of unaffected individuals.[70,77]

Olfactory screening may also be useful in diagnosing PD, although it should not be considered diagnostic by itself because of the multiple etiologies associated with olfactory abnormalities.[94–96] In the future, protein markers obtained from biopsy or other procedures, including spinal fluid, salivary gland, rectal, and colonic samples, may be used as well.[104,105,109,111] In the diagnosis of PD, imaging techniques are primarily used to rule out other neurological disorders; for example, magnetic resonance imaging (MRI) may be used to identify normal-pressure hydrocephalus.[112] Evaluating the anatomy of the substantia nigra (SN) with 7-T MRI may provide a future diagnostic option for identifying patients with PD.[113] Dopamine transporter scans (DaT scans) may be used to differentiate LB-type dementias (PD and DLB) from non-LB dementias, such as Alzheimer's disease.[114–116] Currently, the usefulness of genetic testing in diagnosing PD is debatable because of the lack of clarity on which populations to test, the consequences of the test results, and cost issues.[23–26,117]

CLINICAL PRESENTATION

PD may begin insidiously, with early symptoms presenting in up to 90% of patients in a subtle fashion, such as difficulty getting out of a chair. Nonmotor symptoms may be misinterpreted as related to normal aging or other comorbidities, thereby delaying the diagnosis. The early disease phase lasts approximately four to six years on average and may include nonmotor features, as described previously.[89–94] As the disease progresses, other clinical signs, including thermoregulatory dysfunction, may occur. Although intolerance to cold is common, thermoregulatory abnormalities can also include profuse sweating. Nociceptive (musculoskeletal) and neuropathic pain may occur in some patients in early or later stages of the disease.[79,90–93,118–121] Management of the nonmotor features of PD will be discussed in part 5 of this article.

As noted in the section on diagnosis, the triad of clinical motor features in PD patients includes tremor, rigidity, and bradykinesia. Of these three core features, tremor is most often recognized by patients and caregivers, especially in individuals with the tremor-predominant PD subtype.[71–77,122–125] The motor presentations of PD may correlate with the patient's age at onset; specifically, tremor at onset is twice as common in patients older than 64 years compared with those younger than 45 years of age. In addition, complications related to the duration of treatment—for example, the association of dystonias and dyskinesias with the length of levodopa therapy—are more common in patients diagnosed at younger ages (45 to 55 years old).[77]

Tremor, which often presents as the initial symptom, occurs in approximately two-thirds of PD patients. It typically starts in a mild and intermittent fashion, and is usually measured at a level of 4 Hz to 6 Hz at rest. The usual course is an initial unilateral tremor, which progresses to bilateral involvement over the duration of the disease.[122–125] The tremor of PD is usually described as a resting tremor of the hand (pill-rolling tremor), although it can be present in the lower limbs, toes, and jaws. Stressful situations or asking the patient to perform a mental task may exacerbate and worsen a PD tremor, whereas movement or sleep diminishes the symptoms. Younger patients may have inconsistent presentations or tremor only during periods of fatigue.[122,124] Although resting tremor is the most common type of tremor in PD, some patients may present with action tremor, e.g., tremor manifested during activity. The diagnostic process is further complicated by the presence of mixed tremor, as well as by the fact that patients with benign essential tremor (BET) may develop a resting tremor later in their disease. In imaging studies of PD patients, tremor was not necessarily associated with pathologic dopaminergic loss, and it was actually seen to decline in the later stages of the disease.[68,124] Although tremor is common in PD, it is considered to be the least disabling of the motor features

compared with the other cardinal features—rigidity and bradykinesia.[122,125]

Bradykinesia is a core clinical motor feature of PD and has been defined as a reduction in the speed, gait, and amplitude of a repetitive action involving voluntary movements.[126] Bradykinesia is the most common clinical feature observed in patients with PD and is considered to be a key diagnostic criterion. The disorder usually appears later than tremor, although in some cases it may be the initial symptom and tremor may never develop (i.e., the akinetic–rigid subtype of PD).[123,125] A common clinical presentation associated with this feature is difficulty getting started or initiating movements and a slow, shuffling gait. Patients with bradykinesia may also demonstrate hastening of their gait, in which their walking speed increases with small, rapid steps in an effort to "catch up" with their displaced center of gravity.[123–126] Patients may also experience immobility associated with bradykinesia, typically when confronted by the need to turn or enter through a narrow door.[121] Episodes of "freezing" are an extreme manifestation of PD and usually occur in advanced disease.[125]

The third major cardinal feature of PD is rigidity, which presents as increased muscle tone or amplified resistance to a passive range of motion. The term commonly used to describe this phenomenon in PD patients is "cogwheel rigidity."[72,73,123] This is best described as tension in the muscle, which displays small jerks or a ratchet-like quality when moved passively. Cogwheel rigidity requires an unambiguous diagnosis, since benign essential tremor may also present with a cogwheeling phenomenon.[71,74] The rigidity of PD can affect other body parts besides the limbs, such as the face, which can display a "masked" expression (hypomimia).[73–75,125]

A fourth clinical feature that usually occurs later in the course of PD is postural instability. This symptom has a multifaceted etiology related to other motor symptoms, such as rigidity and neural degeneration in the hypothalamic brainstem or peripheral nervous system. Postural instability can be seriously disabling because of its association with the loss of balance and the risk of falls.[94,120,127]

Other unique features of PD include difficulty with handwriting (e.g., micrographia) and soft speech (hypophonia).[73,74,119,123]

Various staging tools are used to assess the progression of PD and to provide parameters for the use of different management strategies. The most commonly used scale for assessing the clinical status of patients with PD, including both motor and nonmotor symptoms, is the Unified Parkinson's Disease Rating Scale (UPDRS). This four-part tool assesses motor features, psychological features, and activities of daily living in addition to complications related to therapy.[129] Increases of 2.5 and 4.3 points in the UPDRS motor and total scores, respectively, have been recognized as clinically relevant.[129]

Another tool that is not commonly used in clinical practice is the staging scale developed by Hoehn and Yahr, which has been available since the 1960s. In this scale, the degree of impairment is characterized by five stages, ranging from mild symptoms to a bedridden state.[130]

As PD progresses, the patient loses the ability to be independent because of deficits in activities of daily living, thereby necessitating increased caregiver support. The American Academy of Neurology has identified risk factors that may influence the progression of PD. For example, patients who present with tremor as the initial clinical feature may experience a slower disease course and experience a longer response to drug therapy. Men who present with PD in their late 50s or older, or patients who experience motor features and gait problems along with postural instability early in the disease, may experience faster disease progression. Patients who experience a poor response to drug therapy and significant dementia often require early institutional placement.[125,131] Mortality is often associated with complications related to immobility, such as pneumonia, pulmonary embolism, and falls.[10,11,75]

GENERAL APPROACH TO MANAGEMENT

The primary goal in the management of PD is to treat the symptomatic motor and nonmotor features of the disorder, with the objective of improving the patient's overall quality of life. Appropriate management requires an initial evaluation and diagnosis by a multidisciplinary team consisting of neurologists, primary care practitioners, nurses, physical therapists, social workers, and pharmacists.[14,132] It is also important that the patient and his or her family have input into management decisions.[133–135]

Effective management should include a combination of nonpharmacological and pharmacological strategies to maximize clinical outcomes. To date, therapies that slow the progression of PD or provide a neuroprotective effect have not been identified.[135,135] Current research has focused on identifying biomarkers that may be useful in the diagnosis of early disease and on developing future disease-modifying interventions.[136,137]

SUMMARY

PD is a chronic, progressive neurodegenerative disease characterized by both motor and nonmotor features.[1–3] Striatal dopamine depletion has been identified as the major cause of the disorder's motor symptoms,[39–44] which include resting tremor, "cogwheel" rigidity, and bradykinesia.[71–77] Nonmotor symptoms include sleep disorders, depression, and cognitive changes.[4]

The differential diagnosis of PD should include a comprehensive history and physical examination.[65–70] Identifying diseases that have presentations similar to that of PD is an important component of the diagnostic process.[71–77] There are no definitive tests to confirm a diagnosis of PD.[65–70] The UPDRS is the most commonly used scale for assessing the clinical status of PD patients.[129]

The primary goal in the management of PD is to treat the symptomatic motor and nonmotor features of the disorder, with the objective of improving the patient's overall quality of life.[14,132] Therapies that slow the progression of the disease or provide a neuroprotective effect have not been identified.[134,135]

In the next issue of *P&T*, part 2 of this five-part article will discuss the pharmacological management of PD, with a focus on the use of dopaminergic agents.

REFERENCES

1. Parkinson J. *An Essay on the Shaking Palsy*. London: Sherwood, Neely, and Jones; 1817:1–16.
2. Twelves D, Perkins KS, Counsell C. Systematic review of incidence studies of Parkinson's disease. *Mov Disord* 2003;18:19–31.
3. National Institute for Health and Care Excellence (NICE). Parkinson's disease: diagnosis and management in primary and secondary care. NICE clinical guidelines 35. June 2006. Available

at: http://www.nice.org.uk/guidance/cg35/resources/guidance-parkinsons-disease-pdf. Accessed April 28, 2015.
4. Schrag A, Horsfall L, Walters K, et al. Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. *Lancet Neurol* 2015;1:57–64.
5. Parkinson's Disease Foundation. Statistics on Parkinson's. Available at: www.pdf.org.en/parkinson_statistics. Accessed June 19, 2014.
6. Driver JA, Logroscino G, Gaziano JM, et al. Incidence and remaining lifetime risk of Parkinson disease in advanced age. *Neurology* 2009;72:32–38.
7. De Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *Lancet Neurol* 2006;5:525–535.
8. Miller IN, Cronin-Golomb A. Gender differences in Parkinson's disease: clinical characteristics and cognition. *Mov Disord* 2010;25:2695–2703.
9. Rumayor MA, Arrieta O, Sotelo J, et al. Female gender but not cigarette smoking delays the onset of Parkinson's disease. *Clin Neurol Neurosurg* 2009;111:738–741.
10. Gómez-Esteban JC, Zarranz JJ, Lezcano E, et al. Influence of motor symptoms upon the quality of life of patients with Parkinson's disease. *Eur Neurol* 2007;57:161–165.
11. Pennington S, Snell K, Lee M, et al. The cause of death in idiopathic Parkinson's disease. *Parkinsonism Relat Disord* 2010;16:434–437.
12. Jankovic J, Poewe W. Therapies in Parkinson's disease. *Curr Opin Neurol* 2012;25:433–447.
13. Smith Y, Wichmann T, Factor SA, DeLong MR. Parkinson's disease therapeutics: new developments and challenges since the introduction of levodopa. *Neuropsychopharmacology* 2012;37:213–246.
14. Simonson W, Hauser RA, Schapira AHV. Role of the pharmacist in the effective management of wearing-off in Parkinson's disease. *Ann Pharmacother* 2007;41:1842–1849.
15. Van der Marck MA, Bloem BR, Borm GF, et al. Effectiveness of multidisciplinary care for Parkinson's disease: a randomized, controlled trial. *Mov Disord* 2013;28:605–611.
16. Zhou C, Huang Y, Przedborski S. Oxidative stress in Parkinson's disease: a mechanism of pathogenic and therapeutic significance. *Ann NY Acad Sci* 2008;1147:93–104.
17. Logroscino G. The role of early-life environmental risk factors in Parkinson disease: what is the evidence? *Environ Health Perspect* 2005;113:1234–1238.
18. Spatola M, Wider C. Genetics of Parkinson's disease: the yield. *Parkinsonism Relat Disord* 2014;20(suppl 1):S35–S38.
19. Singleton AB, Farer MJ, Bonifati V. The genetics of Parkinson's disease: progress and therapeutic implications. *Mov Disord* 2013;28:14–23.
20. Santiago JA, Scherzer CR, Potashkin JA. Network analysis identifies SOD2 mRNA as a potential biomarker for Parkinson's disease. *PLoS One* 2014;9:e109042.
21. Liu R, Guo X, Park Y, et al. Caffeine intake, smoking, and risk of Parkinson disease in men and women. *Am J Epidemiol* 2012;175:1200–1207.
22. Benmoyal-Segal L, Soreq H. Gene–environment interactions in sporadic Parkinson's disease. *J Neurochem* 2006;97:1740–1755.
23. Van der Merwe C, Haylett W, Harvey J, et al. Factors influencing the development of early- or late-onset Parkinson's disease in a cohort of South African patients. *S Afr Med J* 2012;102:848–851.
24. Wang G, Pan J, Chen SD. Kinases and kinase signaling pathways: potential therapeutic targets in Parkinson's disease. *Prog Neurobiol* 2012;98:207–221.
25. Gilgun-Sherki Y, Djaldetti R, Melamed E, Offen D. Polymorphism in candidate genes: implications for the risk and treatment of idiopathic Parkinson's disease. *Pharmacogenomics J* 2004;4:291–306.
26. Agúndez JA, García-Martín E, Alonso-Navarro H, et al. Anti-Parkinson's disease drugs and pharmacogenetic considerations. *Expert Opin Drug Metab Toxicol* 2013;9:859–874.
27. Marras C, Goldman SM. Genetics meets environment: evaluating gene–environment interactions in neurologic diseases. *Semin Neurol* 2011;31:553–561.
28. Soreq L, Ben-Shaul Y, Israel Z, et al. Meta-analysis of genetic and environmental Parkinson's disease models reveals a common role of mitochondrial protection pathways. *Neurobiol Dis* 2012;45:1018–1030.
29. Curtin K, Fleckenstein AE, Robison RJ, et al. Methamphetamine/amphetamine abuse and risk of Parkinson's disease in Utah: a population-based assessment. *Drug Alcohol Depend* 2015;146:30–38.
30. Chen JJ, Swope DM. Parkinson's disease. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*, 9th ed. New York, New York: McGraw-Hill, 2014.
31. Chade AR, Kasten M, Tanner CM. Nongenetic causes of Parkinson's disease. *J Neural Transm Suppl* 2006;70:147–151.
32. Weisskopf MG, Knekt P, O'Reilly EJ, et al. Persistent organochlorine pesticides in serum and risk of Parkinson's disease. *Neurology* 2010;74:1055–1061.
33. Betarbet R, Sherer TB, MacKenzie G, et al. Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nat Neurosci* 2000;3:1301–1306.
34. Moore DJ, West AB, Dawson VL, Dawson TM. Molecular pathophysiology of Parkinson's disease. *Annu Rev Neurosci* 2005;28:57–87.
35. Martinez TN, Greenamyre JT. Toxin models of mitochondrial dysfunction in Parkinson's disease. *Antioxid Redox Signal* 2012;16:920–934.
36. Langston JW, Ballard P, Tetrud JW, Irwin I. Chronic parkinsonism in humans due to a product of meperidine-analog synthesis. *Science* 1983;219:979–980.
37. Thiruchelvam M, Richfield EK, Baggs RB, et al. The nigrostriatal dopaminergic system as a preferential target of repeated exposures to combined paraquat and maneb: implications for Parkinson's disease. *J Neurosci* 2000;20:9207–9214.
38. Coon S, Stark A, Peterson E, et al. Whole-body lifetime occupational lead exposure and risk of Parkinson's disease. *Environ Health Perspect* 2006;114:1872–1876.
39. Lim SY, Fox SH, Lang AE. Overview of the extranigral aspects of Parkinson disease. *Arch Neurol* 2009;66:167–172.
40. Wolters EC, Braak H. Parkinson's disease: premotor clinicopathological correlations. *J Neural Transm Suppl* 2006;70:309–319.
41. Postuma RB, Aarsland D, Barone P, et al. Identifying prodromal Parkinson's disease: pre-motor disorders in Parkinson's disease. *Mov Disord* 2012;27:617–626.
42. Siderowf A, Lang AE. Premotor Parkinson's disease: concepts and definitions. *Mov Disord* 2012;15:27:608–616.
43. Willis GL, Moore C, Armstrong SM. Breaking away from dopamine deficiency: an essential new direction for Parkinson's disease. *Rev Neurosci* 2012;23:403–428.
44. Jellinger KA. Neuropathology of sporadic Parkinson's disease: evaluation and changes of concepts. *Mov Disord* 2012;27:8–30.
45. Braak H, Del Tredici K, Rub U, et al. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003;24:197–211.
46. Braak H, Braak E. Pathoanatomy of Parkinson's disease. *J Neurol* 2000;247(suppl 2):3–10.
47. Kovari E, Horvath J, Bouras C. Neuropathology of Lewy body disorders. *Brain Res Bull* 2009;80:203–210.
48. Beaulieu JM, Gainetdinov RR. The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacol Rev* 2011;63:182–217.
49. Galvan A, Wichmann T. GABAergic circuits in the basal ganglia and movement disorders. *Prog Brain Res* 2007;160:287–312.
50. Chu J, Wagle-Shukla A, Gunraj C, et al. Impaired presynaptic inhibition in the motor cortex in Parkinson disease. *Neurology* 2009;72:842–849.
51. Caviness JN. Pathophysiology of Parkinson's disease behavior: a view from the network. *Parkinsonism Relat Disord* 2014;20(suppl 1):S39–S43.
52. Del Tredici K, Braak H. Lewy pathology and neurodegeneration in premotor Parkinson's disease. *Mov Disord* 2012;27:597–607.
53. Yasuda T, Mochizuki H. The regulatory role of α-synuclein and parkin in neuronal cell apoptosis: possible implications for the pathogenesis of Parkinson's disease. *Apoptosis* 2010;15:1312–1321.
54. Rohn TT. Targeting alpha-synuclein for the treatment of Parkinson's disease. *CNS Neurol Disord Drug Targets* 2012;11:174–179.
55. Olanow CW. The pathogenesis of cell death in Parkinson's disease. *Mov Disord* 2007;22(suppl 17):S335–S342.
56. Braak H, Bohl JR, Muller CM, et al. The staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered. *Mov Disord* 2006;21:2042–2051.

57. Braak H, Ghebremedhin E, Rub U, et al. Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Res* 2004;318:121–134.
58. Siderowf A, Xie SX, Hurtig H, et al. CSF amyloid β 1-42 predicts cognitive decline in Parkinson disease. *Neurology* 2010;75:1055–1061.
59. Alves G, Lange J, Blennow K, et al. CSF Aβ42 predicts early-onset dementia in Parkinson disease. *Neurology* 2014;82:1784–1790.
60. Moore DJ, West AB, Dawson VL, Dawson TM. Molecular pathophysiology of Parkinson's disease. *Annu Rev Neurosci* 2005;28:57–87.
61. Whitton PS. Inflammation as a causative factor in the aetiology of Parkinson's disease. *Br J Pharmacol* 2007;150:963–976.
62. Kim YS, Joh TH. Microglia, major players in brain inflammation: their roles in the pathogenesis of Parkinson's disease. *Exp Mol Med* 2006;38:333–347.
63. Sawada M, Imamura K, Nagatsu T. Role of cytokines in inflammatory process in Parkinson's disease. *J Neural Transm Suppl* 2006;70:373–381.
64. Tufekci KU, Meuwissen R, Genc S. Inflammation in Parkinson's disease. *Adv Protein Chem Struct Biol* 2012;88:69–132.
65. Caslake R, Moore JN, Gordon JC, et al. Changes in diagnosis with follow-up in an incident cohort of patients with parkinsonism. *J Neurol Neurosurg Psychiatry* 2008;79:1202–1207.
66. Pahwa R, Lyons KE. Early diagnosis of Parkinson's disease: recommendations from diagnostic clinical guidelines. *Am J Manag Care* 2010;16(suppl):S94–S99.
67. Cardoso F. Difficult diagnoses in hyperkinetic disorders: a focused review. *Front Neurol* 2012;3:151. doi: 10.3389/fneur.2012.00151.
68. Kumar H, Jog M. A patient with tremor, part 2: from diagnosis to treatment. *CMAJ* 2011;183:1612–1616.
69. Rigby H, Roberts-South A, Kumar H, et al. Diagnostic challenges revealed from a neuropsychiatry movement disorders clinic. *Can J Neurol Sci* 2012;39:782–788.
70. Grosset DG, Macphee GJA, Nairn M, et al. Diagnosis and pharmacological management of Parkinson's disease: summary of SIGN guidelines. *BMJ* 2010;340:b5614.
71. Baumann CR. Epidemiology, diagnosis and differential diagnosis in Parkinson's disease tremor. *Parkinsonism Relat Disord* 2012;18(suppl 1):S90–S92.
72. Berardelli A, Wenning GK, Antonini A, et al. EFNS/MDS-ES recommendations for the diagnosis of Parkinson's disease. *Eur J Neurology* 2013;20:16–34.
73. Jankovic J. Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry* 2008;79:368–376.
74. Reichmann H. Clinical criteria for the diagnosis of Parkinson's disease. *Neurodegenerative Dis* 2010;7:284–290.
75. Munhoz RP, Werneck LC, Teive HA. The differential diagnosis of parkinsonism: findings from a cohort of 1528 patients and a 10 years comparison in tertiary movement disorders clinics. *Clin Neurol Neurosurg* 2010;112:431–435.
76. Wickremaratchi MM, Knipe MD, Sastry BS, et al. The motor phenotype of Parkinson's disease in relation to age of onset. *Mov Disord* 2011;26:457–463.
77. Suchowersky O, Reich S, Perlmutter J, et al. Practice parameter: diagnosis and prognosis of new onset Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006;66:968–975.
78. Hughes AJ, Daniel SE, Lees AJ. Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease. *Neurology* 2001;57:1497–1499.
79. Quiroga MJ, Carroll DW, Brown TM. Ascorbate- and zinc-responsive parkinsonism. *Ann Pharmacother* 2014;48:1515–1520.
80. López-Sendón J, Mena MA, de Yebenes JG. Drug-induced parkinsonism. *Expert Opin Drug Saf* 2013;12:487–496.
81. López-Sendón JL, Mena MA, de Yébenes JG. Drug-induced parkinsonism in the elderly: incidence, management and prevention. *Drugs Aging* 2012;29:105–118.
82. Lee PE, Sykora K, Gill SS, et al. Antipsychotic medications and drug-induced movement disorders other than parkinsonism: a population-based cohort study in older adults. *J Am Geriatr Soc* 2005;53:1374–1379.
83. Chan HY, Chang CJ, Chiang SC, et al. A randomised controlled study of risperidone and olanzapine for schizophrenic patients with neuroleptic-induced acute dystonia or parkinsonism. *J Psychopharmacol* 2010;24:91–98.
84. Miller DD, Caroff SN, Davis SM, et al. Extrapyramidal side-effects of antipsychotics in a randomised trial. *Br J Psychiatry* 2008;193:279–288.
85. Cortese L, Caligiuri MP, Williams R, et al. Reduction in neuroleptic-induced movement disorders after a switch to quetiapine in patients with schizophrenia. *J Clin Psychopharmacol* 2008;28:69–73.
86. Indo T, Ando K. Metoclopramide-induced parkinsonism. *Arch Neurol* 1982;39:810–893.
87. Miletic V, Relja M. Citalopram-induced parkinsonian syndrome: case report. *Clin Neuropharmacol* 2011;34:92–93.
88. Berg D. Is pre-motor diagnosis possible? The European experience. *Parkinsonism Relat Disord* 2012;18(suppl 1):S195–S198.
89. Meissner WG. When does Parkinson's disease begin? From prodromal disease to motor signs. *Rev Neurol* 2012;168:809–814.
90. Postuma RB, Aarsland D, Barone P, et al. Identifying prodromal Parkinson's disease: pre-motor disorders in Parkinson's disease. *Mov Disord* 2012;27:617–626.
91. Lee CN, Kim M, Lee HM, et al. The interrelationship between non-motor symptoms in atypical parkinsonism. *J Neurol Sci* 2013;327:15–21.
92. Tolosa E, Gaig C, Santamaria J, et al. Diagnosis and the premotor phase of Parkinson disease. *Neurology* 2009;72(suppl):S12–S20.
93. Lang AE. A critical appraisal of the premotor symptoms of Parkinson's disease: potential usefulness in early diagnosis and design of neuroprotective trials. *Mov Disord* 2011;26:775–783.
94. Kang P, Kloke J, Jain S. Olfactory dysfunction and parasympathetic dysautonomia in Parkinson's disease. *Clin Auton Res* 2012;22:161–166.
95. Baba T, Takeda A, Kikuchi A, et al. Association of olfactory dysfunction and brain. metabolism in Parkinson's disease. *Mov Disord* 2011;26:621–628.
96. Ponsen MM, Stoffers D, Booij J, et al. Idiopathic hyposmia as a preclinical sign of Parkinson's disease. *Ann Neurol* 2004;56:173–181.
97. Iranzo A, Molinuevo JL, Santamaria J, et al. Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. *Lancet Neurol* 2007;5:572–577.
98. Boeve BF, Silber MH, Saper CB, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. *Brain* 2007;130:2770–2788.
99. Costa FH, Rosso AL, Maultasch H. Depression in Parkinson's disease: diagnosis and treatment. *Arq Neuropsiquiatr* 2012;70:617–620.
100. Gallagher DA, Schrag A. Psychosis, apathy, depression and anxiety in Parkinson's disease. *Neurobiol Dis* 2012;46:581–589.
101. Huot P, Fox SH, Brotchie JM. The serotonergic system in Parkinson's disease. *Prog Neurobiol* 2011;95:163–212.
102. Delaville C, Deurwaerdère PD, Benazzouz A. Noradrenaline and Parkinson's disease. *Front Syst Neurosci* 2011;5:31. doi: 10.3389/fnsys.2011.00031.
103. Bohnen NI, Albin RL. The cholinergic system and Parkinson disease. *Behav Brain Res* 2011;221:564–573.
104. Chahine LM, Stern MB, Chen-Plotkin A. Blood-based biomarkers for Parkinson's disease. *Parkinsonism Relat Disord* 2014;20(suppl 1):S99–S103.
105. Sharma S, Moon CS, Khogali A, et al. Biomarkers in Parkinson's disease (recent update). *Neurochem Int* 2013;63:201–229.
106. Donadio V, Incensi A, Leta V, et al. Skin nerve α synuclein deposits: a biomarker for idiopathic Parkinson disease. *Neurology* 2014;82:1362–1369.
107. Double KL, Rowe DB, Carew-Jones FM, et al. Anti-melanin antibodies are increased in sera in Parkinson's disease. *Exp Eurol* 2009;217:297–301.
108. American Academy of Neurology. A saliva gland test for Parkinson's disease? January 10, 2013. Available at: http://www.aan.com/pressroom/home/pressrelease/1130. Accessed April 29, 2015.
109. Hall S, Ohrfelt A, Constantinescu R, et al. Accuracy of a panel of 5 cerebrospinal fluid biomarkers in the differential diagnosis of patients with dementia and/or parkinsonian disorders. *Arch Neuro* 2012;69:1445–1452.
110. Berg D, Hochstrasser H, Schweitzer KJ, Riess O. Disturbance of iron metabolism in Parkinson's disease ultrasonography as a biomarker. *Neurotox Res* 2006;9:1–13.

continued on page 532

continued from page 510

111. Pouclet H, Lebouvier T, Coron E. A comparison between rectal and colonic biopsies to detect Lewy pathology in Parkinson's disease. *Neurobiol Dis* 2012;45:305–309.
112. Baglieri A, Marino MA, Morabito R, et al. Differences between conventional and nonconventional MRI techniques in Parkinson's disease. *Funct Neurol* 2013;28:73–82.
113. Cosottini M, Frosini D, Pesaresi I, et al. MR imaging of the substantia nigra at 7 T enables diagnosis of Parkinson disease. *Radiology* 2014;271:831–838.
114. Guilloteau D, Chalon S. PET and SPECT exploration of central monoaminergic transporters for the development of new drugs and treatments in brain disorders. *Curr Pharm Des* 2005;11:3237–3245.
115. Bajaj N, Hauser RA, Grachev ID. Clinical utility of dopamine transporter single photon emission CT (DaT-SPECT) with (123I) ioflupane in diagnosis of parkinsonian syndromes. *J Neurol Neurosurg Psychiatry* 2013;84:1288–1295.
116. Kägi G, Bhatia KP, Tolosa E. The role of DAT-SPECT in movement disorders. *J Neurol Neurosurg Psychiatry* 2010;81:5–12.
117. Ozelius LJ, Senthil G, Saunders-Pullman R, et al. LRRK2 G2019S as a cause of Parkinson's disease in Ashkenazi Jews. *N Engl J Med* 2006;354:424–425.
118. Jain S, Goldstein DS. What ARE Parkinson disease? Non-motor features transform conception of the shaking palsy. *Neurobiol Dis* 2012;46:505–507.
119. Maetzler W, Hausdorff JM. Motor signs in the prodromal phase of Parkinson's disease. *Mov Disord* 2012;27:627–633.
120. Doherty KM, van de Warrenburg BP, Peralta MC, et al. Postural deformities in Parkinson's disease. *Lancet Neurol* 2011;10:538–549.
121. Mendonca DA: Tasks of attention augment rigidity in mild Parkinson disease. *Can J Neurol Sci* 2008;35:501–505.
122. Jiménez MC, Vingerhoets FJ. Tremor revisited: treatment of PD tremor. *Parkinsonism Relat Disord* 2012;18(suppl 1):S93–S95.
123. Garcia Ruiz PJ, Catalán MJ, Fernández Carril JM. Initial motor symptoms of Parkinson disease. *Neurologist* 2011;17(suppl 1):S18–S20.
124. Hallett M. Parkinson's disease tremor: pathophysiology. *Parkinsonism Relat Disord* 2012;18(suppl 1):S85–S86.
125. Xia R, Mao ZH. Progression of motor symptoms in Parkinson's disease. *Neurosci Bull* 2012;28:39–48.
126. Grabli D, Karachi C, Welter ML, et al. Normal and pathological gait: what we learn from Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2012;83:979–985.
127. Pfeiffer RF. Autonomic dysfunction in Parkinson's disease. *Expert Rev Neurother* 2012;12:697–706.
128. The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations. *Mov Disord* 2003;18:738–750.
129. Shulman LM, Gruber-Baldini AL, Anderson KE, et al. The clinically important difference on the unified Parkinson's disease rating scale. *Arch Neurol* 2010;67:64–70.
130. Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. *Neurology* 1967;17:427–442.
131. Antonini A, Barone P, Marconi R. The progression of non-motor symptoms in Parkinson's disease and their contribution to motor disability and quality of life. *J Neurol* 2012;259:2621–2631.
132. Van der Marck MA, Bloem BR. How to organize multispecialty care for patients with Parkinson's disease. *Parkinsonism Relat Disord* 2014;20(suppl 1):S167–S173.
133. Politis M, Wu K, Molloy S, et al. Parkinson's disease symptoms: the patient perspective. *Mov Disord* 2010;25:1646–1651.
134. Fernandez HH. Updates in the medical management of Parkinson disease. *Cleve Clin J Med* 2012;79:28–35.
135. Uitti RJ. Treatment of Parkinson's disease: focus on quality of life issues. *Parkinsonism Relat Disord* 2012;18(suppl 1):S34–S36.
136. Montgomery EB Jr. Practice parameter: neuroprotective strategies and alternative therapies for Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2007;68:164.
137. Sozio P, Cerasa LS, Abbadessa A, et al. Designing prodrugs for the treatment of Parkinson's disease. *Expert Opin Drug Discov* 2012;7:385–406. ■